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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/402,260 | 09/30/1999 | ERIC H. KAWASHIMA | 018428-0004U | 5717 |

7590 01/24/2002

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| EXAMINER | |
|---|---|
| MYERS, CARLA J | |
| ART UNIT | PAPER NUMBER |
| 1655 | |

DATE MAILED: 01/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/402,260 | Applicant(s) KAWASHIMA ET AL. | |
|---|---|---|---|
| | Examiner Carla Myers | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *04 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-17,21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-17,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The request filed on January 4, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/402,260 is acceptable and a CPA has been established. An action on the CPA follows.

2. The previous grounds of rejection are withdrawn in view of Applicants amendment filed November 7, 2001. The following contains new grounds of rejection.

3. Claims 1, 2, 4-17, 21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 4-17 are indefinite over the recitation of "such bases" because this phrase is vague and does not specify the identity of the base. The claims should be amended to refer to the complementary bases.

Claims 1, 2, and 4-17 are indefinite over the recitations of "each location" and "at these locations" because these phrases are unclear since they do not specify a particular location. The claims should be amended to refer to the first and second locations.

Claim 2 is indefinite and confusing over the recitation of "converting all or part of the sequence obtained in step e) to its complementary sequence". It is not clear as to what is intended to be meant by "converting" because this is not an art recognized term to describe the synthesis of nucleic acids. Furthermore, it is unclear as to whether this step refers to the additional extension of the primer to form an extended double-stranded nucleic acid or whether

this step refers to separating the extended primer from the template and then synthesizing a copy of the extended primer.

Claims 21 and 23 are indefinite over the recitation of "the hybridized target nucleic acid/primer" because this phrase lacks proper antecedent basis. The claim should be amended so that step (a) clarifies that the process step results in the formation of a "hybridized target nucleic acid/primer".

Claims 21 and 23 are indefinite over the recitation of "the incremental base additions" because this phrase lacks proper antecedent basis. While the claim previously refers to "incremental label incorporated into the primer" and recites a process step in which a nucleotide bearing a label is incubated with a target nucleic acid/primer complex, the claims do not previously refer to a step of incorporating a base.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 4-15, 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Rosenthal (U.S. Patent No. 6,087,095).

Rosenthal teaches a method for sequencing nucleic acids comprising the steps of providing at multiple locations, a plurality of nucleic acid molecules hybridized to a primer to

form target nucleic acid/primer complexes; contacting the target nucleic acid/primer complexes with a DNA polymerase and labeled nucleotides to allow for extension of the primer if a complementary nucleotide or plurality of nucleotides is present at the appropriate position in the target nucleic acid; detecting whether the labeled nucleotide is incorporated into the extended primer in order to determine the sequence of the target nucleic acid (see, for example, columns 7-8). In particular, Rosenthal (see column 7, lines 27-41) states that "(i)n an alternative embodiment of the invention, steps (c) and (d) of the first aspect of the invention are repeated sequentially a plurality of times before removal or neutralization of the label. The number of times that steps (c) and (d) can be repeated depends on the sensitivity of the apparatus used to detect when a labeled nucleotide has been added onto the primer". The method detects incorporation of at least 4-16 labeled nucleotides, with more sensitive devices being capable of detecting additional labeled nucleotides (columns 7-8). The nucleotide may be labeled with a radioactive or fluorescent moiety and is detectable by absorption or emission methods (columns 6 and 11). Rosenthal teaches that the sequencing method may be performed using labeled and unlabeled nucleotides and using a combination of dATP, dGTP, dCTP and dTTP or dUTP (column 6 and 8). With respect to claim 4, Rosenthal teaches removing excess unincorporated nucleotides by washing (see e.g., column 7, line 59 and column 11, lines 1 and 2). With respect to claims 5 and 14, the reference teaches immobilizing the primer or target nucleic acid onto a solid support (column 4, lines 23-65) and detecting the labeled nucleotide without moving the extended primer to a different location (see, for example, column 11). The reference further

teaches that the sequencing method provides the advantage of allowing several DNA clones to be processed in parallel (column 3, lines 58-59) and particularly teaches method which allow for the simultaneous sequencing of $10^4$ clones.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal in view of Fu (Nucleic Acids Research (Feb 1997) 25:677-679; reference 'AK').

Rosenthal teaches a method for sequencing nucleic acids comprising the steps of providing at multiple locations, a plurality of nucleic acid molecules hybridized to a primer to form target nucleic acid/primer complex; contacting the target nucleic acid/primer complexes with a DNA polymerase and labeled nucleotides to allow for extension of the primer if a

complementary nucleotide or plurality of nucleotides is present at the appropriate position in the target nucleic acid; detecting whether the labeled nucleotide is incorporated into the extended primer, thereby determining sequence of the target nucleic acid (see, for example, columns 7-8). In particular, Rosenthal (see column 7, lines 27-41) states that "(i)n an alternative embodiment of the invention, steps (c) and (d) of the first aspect of the invention are repeated sequentially a plurality of times before removal or neutralization of the label. The number of times that steps (c) and (d) can be repeated depends on the sensitivity of the apparatus used to detect when a labeled nucleotide has been added onto the primer". The method detects incorporation of at least 4-16 labeled nucleotides, with more sensitive devices being capable of detecting additional labeled nucleotides (columns 7-8). The nucleotide may be labeled with a radioactive or fluorescent moiety and is detectable by absorption or emission methods (columns 6 and 11). Rosenthal teaches that the sequencing method may be performed using a suitable ratio of labeled and unlabeled nucleotides and using a combination of dATP, dGTP, dCTP and dTTP or dUTP (column 6 and 8). The reference further teaches that the sequencing method provides the advantage of allowing several DNA clones to be processed in parallel (column 3, lines 58-59) and particularly teaches methods which allow for the simultaneous sequencing of $10^4$ clones. Rosenthal teaches hybridizing an oligonucleotide to the target nucleic acid to prime the extension reaction. Rosenthal does not teach using double-stranded DNA having nicks to prime the extension reaction.

Fu teaches methods for sequencing target nucleic acids wherein the methods utilize a double-stranded nucleic acid that has been nicked to provide a 3' terminus which serves as a primer during the sequencing reaction. Fu teaches that the use of nicked double-stranded DNA for sequencing avoids the need to prepare and isolate single-stranded DNA and the need to synthesize primers, and avoids problems that arise due to secondary structure formation in single-stranded DNA (see page 679).

In view of the teachings of Fu, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rosenthal so as to have utilized nicked DNA as the template for sequencing rather than using a primer hybridized to the target DNA in order to have provided a highly effective template for sequencing a target nucleic acid and to have provided a simpler, more rapid means for sequencing which did not require generating single-stranded DNA or oligonucleotide primers and which would avoid problems associated with secondary structure formation that occurs when sequencing ssDNA molecules.

6. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal in view of Rabani (WO 96/27025; reference 'AH').

Rosenthal teaches a method for sequencing nucleic acids comprising the steps of providing at multiple locations, a plurality of nucleic acid molecules hybridized to a primer to form target nucleic acid/primer complexes; contacting the target nucleic acid/primer complexes with a DNA polymerase and labeled nucleotides to allow for extension of the primer if a complementary nucleotide or plurality of nucleotides is present at the appropriate position in the

target nucleic acid; detecting whether the labeled nucleotide is incorporated into the extended primer in order to determine the sequence of the target nucleic acid (see, for example, columns 7-8). In particular, Rosenthal (see column 7, lines 27-41) states that "(i)n an alternative embodiment of the invention, steps (c) and (d) of the first aspect of the invention are repeated sequentially a plurality of times before removal or neutralization of the label. The number of times that steps (c) and (d) can be repeated depends on the sensitivity of the apparatus used to detect when a labeled nucleotide has been added onto the primer". The method detects incorporation of at least 4-16 labeled nucleotides, with more sensitive devices being capable of detecting additional labeled nucleotides (columns 7-8). The nucleotide may be labeled with a radioactive or fluorescent moiety and is detectable by absorption or emission methods (columns 6 and 11). Rosenthal teaches that the sequencing method may be performed using labeled and unlabeled nucleotides and using a combination of dATP, dGTP, dCTP and dTTP or dUTP (column 6 and 8). The reference further teaches that the sequencing method provides the advantage of allowing several DNA clones to be processed in parallel (column 3, lines 58-59) and particularly teaches method which allow for the simultaneous sequencing of $10^4$ clones. Rosenthal teaches immobilizing a plurality of the same target nucleic acid at a particular location. Rosenthal does not teach immobilizing only one nucleic acid molecule at location.

Rabani (pages 7-8) teaches methods for sequencing nucleic acids comprising the steps of providing at multiple locations, a single nucleic acid molecule having a 3' terminus that may serve as a primer in a primer extension reaction; contacting the target nucleic acid molecule with

a DNA polymerase and labeled nucleotides to allow for extension of the primer if a complementary nucleotide or plurality of nucleotides is present at the appropriate position in the target nucleic acid; and detecting whether the labeled nucleotide is incorporated into the extended primer to thereby determine the sequence of the target nucleic acid. Rabani (page 7) teaches that sequencing with "the distinct single-molecule regime rather than with populations of identical molecules provides substantial advantages of parallelism, facility of use and implementation (including automated implementation) and operability."

In view of the teachings of Rabani, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rosenthal so as to have utilized single nucleic acid molecules rather than a plurality of identical nucleic acid molecules for sequencing in order to have achieved the benefits set forth by Rabani of improved parallelism, implementation and operability.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER

January 22, 2002